Risk factors associated with alterations in carotid intima–media thickness in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis

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Background **The possibility that calcium antagonists exert an anti-atherosclerotic action at least partly independently of the blood-pressure-lowering effect is supported by results of a large number of experimental studies and can now be investigated by quantitative B-mode ultrasound imagining of the carotid artery walls.**

Design **The European Lacidipine Study on Atherosclerosis (ELSA) is a prospective, randomized, double-blind, multinational trial comparing effects of 4-year treatment based on the long-acting, highly lipophilic calcium antagonist lacidipine with those of treatment based on the β-blocker atenolol on the development of carotid artery wall alterations in patients (aged 45–75 years) with mild-to-moderate hypertension (systolic blood pressure 150–210 mmHg and diastolic blood pressure 95–115 mmHg). While the intervention study is progressing, this article summarizes baseline data obtained from the whole cohort of 2259 patients randomly allocated to treatment.**

Methods **Baseline ultrasound data were obtained from two replicate examinations performed shortly before random allocation to treatment by certified sonographers at 23 referral centres and read at the ultrasound coordinating centre at the Wake Forest University School of Medicine. Intima–media thickness was measured at up to 12 different sites in the carotid artery tree and expressed as the mean of the maxima at these sites (M_{max}), the mean of the maxima at four sites in the distal common carotid artery and bifurcation (CBM_{max}) and the maximum intima–media thickness (T_{max}). Baseline demographic and clinical measurements were performed by investigators in 410 peripheral clinical units and 24 h ambulatory blood pressure monitorings read and validated by members of a centralized unit at the University of Milan. The statistical analysis centre at the Technische Universität München received and analysed all baseline data, by calculating means ± SD, medians and ranges and performing correlation (Spearman correlation coefficients) and multiple regression analyses.**

Results **Prevalence of carotid artery wall alterations among the hypertensive patients randomly allocated to treatment in the ELSA was very high: 82% had $T_{max} \geqslant 1.0$ mm ('plaques' according to protocol) and 17% had $T_{max} \geqslant 1.0$ and < 1.3 mm ('thickening'), with a median of two plaques per patient. We found significant correlations between ultrasound measurements and the following demographic and clinical variables: age, sex, systolic blood pressure and pulse pressure (both clinic and ambulatory), concentrations of total, high-density lipoprotein and low-density lipoprotein cholesterol and triglycerides, smoking habit and duration of hypertension. We found no significant correlation to diastolic blood pressure and glucose concentration. A multiple regression analysis indicated significant variables in the following rank order: age, 24 h ambulatory pulse pressure, sex, low-density lipoprotein cholesterol concentration, triglyceride concentration, smoking and clinic systolic blood pressure.**

Conclusions **Analysis of baseline data from the ELSA has shown that there is an extremely marked prevalence of carotid artery wall alterations among mild-to-moderate, middle-aged hypertensive patients. In addition to age, systolic blood pressure and pulse pressure, particularly if they are accurately measured by ambulatory monitoring, play a major role, somewhat greater than those of sex, low-density lipoprotein cholesterol concentration and smoking, in influencing intima–media thickness.**
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Introduction

Background and rationale of the European Lacidipine Study on Atherosclerosis (ELSA)

Many randomized trials have now provided very convincing evidence that antihypertensive therapy does effectively lower the incidence of hypertension-related cardiovascular events [1–3], but it has been remarked that event-based trials, although they are fundamental in demonstrating benefits of antihypertensive therapy, cannot bring forth information on the ability of this therapy to influence various types of cardiovascular injury preceding and underlying events [4].

The possibility that antihypertensive drugs, or at least a few classes of antihypertensive drugs, in particular calcium antagonists and angiotensin converting enzyme inhibitors, exert an anti-atherosclerotic action that is at least partly independent of the blood-pressure-lowering effect is supported by a large body of evidence obtained from several experimental models of atherosclerosis [5]. Quantitative B-mode ultrasound imaging has recently been shown to be a valid, sensitive and reproducible non-invasive method for assessing morphological changes in the carotid artery wall known to be associated with early atherosclerosis [6,7]. It has been used in two randomized trials, both comparing a calcium antagonist with a diuretic agent. The two trials, of a relatively small size, have led to apparently different conclusions, one, the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS, with 883 hypertensive patients), that the calcium antagonist isradipine and the diuretic hydrochlorothiazide have a very similar effect on progression of carotid artery wall lesions [8], the other, the Verapamil Hypertension Atherosclerosis Study (VHAS, with 494 hypertensive patients), that the calcium antagonist verapamil had a significantly greater influence than did the diuretic chlorthalidone on regression of carotid artery wall lesions [9].

ELSA [10,11] has been planned as a much larger randomized study using the same ultrasound methodology; furthermore, the calcium antagonist chosen for randomized comparison with the β-adrenergic blocker atenolol is lacidipine, a slow-onset, long-acting, highly lipophilic dihydropyridine, that has been shown to be quite effective in retarding progression of atherosclerosis lesions in several experimental models [12].

Design, objectives, and organization of ELSA

These have more extensively been reported in previous publications [10,11,13–17] and will be summarized here insofar as they are relevant to the present article describing baseline characteristics of all subjects randomly allocated to treatment in ELSA. In brief, ELSA is a prospective, randomized, double-blind, multinational trial comparing effects of 4-year treatment based on the calcium antagonist lacidipine with those of treatment based on the β-blocker atenolol on the development of carotid artery wall alterations in patients with mild-to-moderate hypertension.

We included in our study subjects of both sexes, aged 45–75 years, with sitting systolic blood pressure (SBP) 150–210 mmHg and diastolic blood pressure (DBP) 95–115 mmHg, fasting serum total cholesterol concentration $\leqslant$ 320 mg/dl, fasting serum triglyceride concentration $\leqslant$ 300 mg/dl, serum creatinine concentration $\leqslant$ 1.7 mg/dl and a readable ultrasound carotid artery scan with maximum intima–media thickness (IMT) no greater than 4.0 mm. The main exclusion criteria were a recent myocardial infarction or stroke and insulin-dependent diabetes mellitus.

Double-blind randomized treatment with lacidipine was initiated with a dose of 4 mg once daily, and brought to 6 mg once daily if, after 1 month, DBP had not been lowered to $\leqslant$ 90 mmHg; the initial dose of atenolol was 50 mg once daily, to be brought to 100 mg once daily if DBP had not been lowered to $\leqslant$ 90 mmHg. Subsequently, if this DBP goal had not been attained, 12.5–25 mg hydrochlorothiazide once daily could be added. Randomly allocated treatment is to be maintained for a minimum period of 4 years.

Before randomization and subsequently every year two replicate B-mode ultrasound scans of the carotid arteries and 24 h blood pressure monitoring are to be performed at 23 referral centres, as detailed in Methods.

Patients were recruited by 410 clinical units in seven European countries (France, Germany, Greece, Italy, Spain, Sweden and UK). These units also perform clinic measurements of sitting blood pressure and heart rate and clinical examination of all subjects at 6-month intervals throughout the trial. All forms with clinical and laboratory data are collected by monitors and sent to a data management centre, responsible for the continuous delivery of data to the statistical analysis centre at the Institute of Medical Statistics and Epidemiology, Technische Universität, Munich, Germany, which also analyses all data received from the ultrasound centre and the centralized ambulatory blood pressure calculation unit.

The primary objective of ELSA is a comparison of the effects of the two randomly allocated treatments on changes in carotid artery IMT during 4 years. A secondary objective is to compare the effects of the two treatments on the incidence of major cardiovascular events. The primary end point for treatment efficacy analysis is the change in the carotid IMT, measured as the mean of the maximum IMT of the four far walls of the carotid bifurcations and distal common carotid arteries (defined as CBM_{max}). Changes in the mean thickness of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid,

defined as M_{max}), in the overall mean maximum IMT (defined as T_{max}) and in the segment with the greatest change elicited by treatment will also be analysed as secondary end points. Final efficacy analyses will be conducted without stratification of patients and baseline IMT will be used as a covariate. The calculation of sample size required was based on the following assumptions: change in CBM_{max}, $\alpha = 5\%$, power 90%, $\delta = 0.04$ mm/year, $\sigma = 0.1939$ mm and drop-out rate 35%. This calculation resulted in a total number of 1520 patients (760 patients for each treatment) to be randomly allocated. A decision to increase the sample size to at least 2000 patients was taken in order to increase the statistical power of the final analysis. In the present article we report baseline data obtained from all randomly allocated patients and correlation analyses performed with particular attention to all IMT measurements considered end-points in the ELSA protocol.

Methods

Ultrasound examinations

Details on the protocols for ultrasound examinations and readings in ELSA have been reported elsewhere [15]. All baseline data described here were obtained from two replicate examinations performed between visits 0 and 1 by certified sonographers at 23 referral centres and read at the ultrasound coordinating centre at the Division of Vascular Ultrasound Research of the Wake Forest University Medical Center, Winston Salem, North Carolina, USA. They have been expressed as CBM_{max}, M_{max} and T_{max}, according to the definitions given above, and calculated as averages of two replicate measurements. T_{max} values have also been used to categorize patients into three strata [stratum I (plaques) $T_{max} \geqslant 1.3$ mm, stratum II (thickening) $T_{max} < 1.3$ mm but $\geqslant 1.0$ mm and stratum III (normal) $T_{max} < 1.0$ mm] and to identify the number and location of IMT $\geqslant 1.3$ mm ('plaques') in various segments of the carotid artery tree. IMT averages have also been calculated for various carotid segments.

Demographic and clinical measurements

Before random allocation to treatment of patients (visits 0–1) investigators in peripheral clinical units completed standard forms indicating the patient's initials, sex, age (years), race, weight (kg), height (m), estimated duration of hypertension (years), smoking habits (smoker, former smoker or non-smoker), relevant past medical history (cardiovascular and non-cardiovascular), previous antihypertensive medication (withdrawn at visit 0) and concomitant medication (at visit 0 and, separately, at visit 1). Body mass index (BMI) was calculated as weight/height^2. During visit 1, after a 4-week wash-out from previous antihypertensive medication and immediately before random allocation to treatment, sitting clinic blood pressure was measured by using a mercury manometer three consecutive times during no less than 5 min after the patients had been seated comfortably for at least 5 min. The average of these three measurements was used for further analyses. Pulse pressure was calculated as the difference between SBP and DBP. Heart rate was calculated from the radial pulse during 30 s. Serum concentrations of creatinine, glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured from blood samples drawn during visit 0; measurements (in mg/dl) were performed according to standard laboratory methods in peripheral laboratories near the clinical units. Low-density lipoprotein (LDL) cholesterol concentration was calculated according to the standard formula and LDL : HDL ratio was also calculated.

Ambulatory blood pressure monitoring

Baseline data were obtained from 25 h monitoring performed after a period of wash-out from previous antihypertensive medication before random allocation to treatment, using the techniques described before [17]. Diskettes with patients' recordings were edited at the centralized ambulatory blood pressure calculation unit at the Centro di Fisiologia Clinica e Ipertensione, University of Milan, Ospedale Maggiore, to remove artefacts according to criteria that had been determined beforehand [18] and to verify completeness and quality of the monitored data. Computer programs were used to obtain average 24 h, daytime (0600–0000 h) and night-time (0000–0600 h) values for each of SBP, DBP, pulse pressure and heart rate.

Statistical analysis

For all demographic, clinical, laboratory, blood pressure (clinic and ambulatory) and carotid ultrasound data means ± SD or medians (ranges) were calculated for data from all evaluable patients. For non-continuous variables frequency distributions were provided. There were two baseline ultrasound measurements for each patient. The average of these measurements was used for further analyses. In particular, for categorization into strata, a patient was considered to have a plaque if the average of the two T_{max} values was $\geqslant 1.3$ mm; the number of plaques per patient was calculated by counting the sites with maximum IMT $\geqslant 1.3$ mm, both for the first and for second measurement, and averaging the results. Correlation analyses were separately performed for relationships between ultrasound data (expressed as CBM_{max}, M_{max}, mean T_{max} and number of plaques per patient) and various blood pressures and demographic and laboratory variables usually considered risk factors for cardiovascular disease. Correlations were also calculated for relationships between serum metabolic variables and blood pressure values. Correlations were expressed as Spearman correlation coefficients and P values were calculated. Age-adjusted partial correlation coefficients were also calculated. IMT measurements for various subgroups, defined by sex, smoking habit and previous cardiovascular diagnoses (yes/no) were analysed. The differences between the groups were

assessed by using non-parametric tests (Wilcoxon test for two independent groups and Kruskal–Wallis test for more than two independent groups).

Multiple regression analyses were performed separately for the three key variables CBM_{max}, M_{max} and T_{max}. A set of independent variables was identified with age, sex, BMI, smoking status, previous antihypertensive medication, previous cardiovascular diagnoses, clinic SBP, DBP and heart rate, the SBP–heart rate product, 24 h ambulatory SBP, DBP, pulse pressure and heart rate and serum total cholesterol concentration, HDL cholesterol concentration, LDL cholesterol concentration, LDL : HDL cholesterol ratio, triglyceride concentration, glucose concentration and creatinine concentration. In a first step a simple analysis for correlation of the independent variables was performed and classes of variables with high correlations were identified. By selecting a representative of each of the classes the problem of multicollinearity was avoided. This procedure resulted in the selection of the variables age, sex, smoking status, BMI, glucose concentration, LDL cholesterol concentration, HDL cholesterol concentration, triglyceride concentration, 24 h ambulatory pulse pressure and heart rate, clinic SBP, creatinine concentration, previous antihypertensive medication and previous cardiovascular diagnoses (yes/no). These were used for a backwards elimination strategy, resulting in identification of those variables with P values < 0.05. Finally, the significant independent variables were ordered according to their standardized effect, defined as regression coefficient/standard error of the regression coefficient. Multiple regression analyses were performed using original values of IMT variables, after logarithmic transformation and after transformation of CBM_{max} and M_{max} to $1/\sqrt{CBM_{max}}$ and $1/\sqrt{M_{max}}$, the latter transformation giving normally distributed values. In addition to the multiple regressions based on the data from patients for whom we had complete information on all variables (complete case analyses), two strategies were also deployed to handle missing values of the independent variables. In the first strategy missing values were substituted by the corresponding mean of the variable; in the second strategy by estimation of the independent variable from the remaining independent variables. As mentioned before, multiple tests were performed: the corresponding P values have to be handled with care and interpreted cautiously because no formal multiple test procedure was used to control the overall level of significance.

Results

Recruitment of hypertensive patients for the ELSA trial began in June 1994 and ended in November 1995, after 2259 subjects had been allocated randomly to treatment.

Demographic and clinical characteristics at baseline

These are summarized in Tables 1 and 2. In Table 1 prevalence of non-continuous variables is indicated as number and percentage of patients with a given characteristic. In Table 2 means and SD are listed for continuous variables. Of our patients, 54% were men, almost all were Caucasian and 21% were current smokers (Table 1). Few had a history of cardiovascular disease (n = 289, 12.8%) and only 55 of these 289 patients reported having previously suffered from major cardiovascular disease (myocardial infarction, angina pectoris, a stroke, coronary bypass surgery or angioplasty, congestive heart failure and peripheral arterial disease). Of the randomly allocated patients, 62.4% had previously been administered antihypertensive therapy that was withdrawn at visit 0; less than 10% had maintained some concomitant (non-antihypertensive) medication at random allocation to treatment. Patients had a mean age of 56 years (14.5% of patients were older than 65 years), were moderately overweight (but only 20.6% had BMI $\geqslant 30\ kg/m^2$) and had moderately elevated sitting SBP and DBP (164/101 mmHg; Table 2). At random allocation to treatment previously treated patients (from whom therapy had been withdrawn for at least 4 weeks) had slightly higher SBP (but not DBP) values than did previously untreated patients. Ambulatory blood pressure values were available for 1891 subjects (83.7% of all randomly allocated patients). Twenty-four-hour average SBP and DBP values

Table 1 Baseline patient characteristics: non-continuous variables

All patients	2259 (100)
Countries of recruitment	
France	342 (15.1)
Germany	425 (18.8)
Greece	129 (5.7)
Italy	797 (35.3)
Spain	131 (5.8)
Sweden	260 (11.5)
UK	175 (7.8)
Men	1225 (54.2)
Race	
Caucasian	2218 (98.4)
Non-Caucasian	35 (1.6)
Smoking habit	
Non-smoker	1263 (56.4)
Former smoker	509 (22.7)
Smoker	468 (20.9)
Medical history	
Cardiovascular	289 (12.8)
Non-cardiovascular	1311 (58.0)
Major cardiovascular	55 (2.4)
Previous antihypertensive therapy	
Diuretics	82 (3.6)
β-Blockers	238 (10.5)
Antihypertensives including ACE inhibitors	363 (16.1)
Vasodilators including calcium antagonists	298 (13.2)
Others	5 (0.2)
Combination therapy	422 (18.7)
None	851 (37.7)
Concomitant medication	
Visit 0	876 (38.8)
Visit 1 (random allocation)	213 (9.4)

Values are expressed as numbers of patients (percentages). Data were obtained during visit 0 (beginning of placebo run-in period) for patients subsequently randomly allocated treatment (at visit 1). Previous antihypertensive therapy indicates patients from whom antihypertensive therapy was withdrawn at visit 0. Concomitant medication indicates patients being administered non-antihypertensive therapy at visit 0 and, separately, at visit 1. ACE, angiotensin converting enzyme.

Table 2 **Baseline patient characteristics: continuous variables**

Variable	Patients (n)	Value
Age (years)	2251	56.1 ± 7.8
BMI (kg/m^2)	2249	27.2 ± 3.8
Duration of hypertension (years)	1829	7.0 ± 6.3
Clinic sitting blood pressure and heart rate		
SBP (mmHg)	2258	163.6 ± 12.6
DBP (mmHg)	2258	101.3 ± 5.3
Pulse pressure (mmHg)	2258	62.3 ± 11.5
SBP, previously treated (mmHg)	1408	164.5 ± 12.4
SBP, previously untreated (mmHg)	817	162.2 ± 12.9
DBP, previously treated (mmHg)	1408	101.3 ± 5.2
DBP, previously untreated (mmHg)	817	101.4 ± 5.4
Heart rate (beats/min)	2254	76.2 ± 9.2
Ambulatory blood pressure and heart rate		
24 h SBP (mmHg)	1891	141.0 ± 14.5
24 h DBP (mmHg)	1891	87.9 ± 9.5
24 h pulse pressure (mmHg)	1891	53.1 ± 10.0
24 h heart rate (beats/min)	1891	74.2 ± 9.0
Serum concentrations (mg/dl)		
Total cholesterol	2077	224.9 ± 38.4
HDL cholesterol	1882	51.3 ± 16.7
LDL cholesterol	1870	147.2 ± 36.1
LDL : HDL cholesterol ratio	1870	3.2 ± 1.4
Triglycerides	2061	135.1 ± 69.5
Glucose	2240	96.4 ± 20.4
Creatinine	1941	1.0 ± 3.1

Values are expressed as means ± SD of variables determined during visit 0 (beginning of placebo run-in period) namely age, body mass index (BMI), duration of hypertension and metabolic variables, during visit 1 (clinic blood pressure and heart rate) or between visits 0 and 1 (ambulatory blood pressure and heart rate). Individual clinic blood pressure values are averages of three consecutive measurements, individual ambulatory blood pressure and heart rate values are averages of all measurements performed during 24 h. n, the number of patients for whom a given measurement was available; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

were consistently lower than clinic sitting SBP and DBP, with daytime values definitely higher than night-time values. Metabolic data were available for 83–99% of randomly allocated patients: means and SD are indicated in Table 2. Overall 25.7% of subjects had total cholesterol concentrations higher than 250 mg/dl, 3.1% had HDL cholesterol concentrations lower than 30 mg/dl, 35.3% had LDL cholesterol concentrations higher than 160 mg/dl, 15.1% had triglyceride concentrations higher than 200 mg/dl, and 7.4% had fasting glucose concentrations higher than 120 mg/dl.

Ultrasound carotid artery wall measurements at baseline

The means, SD, medians and ranges of baseline values of the IMT parameters used as major end points in ELSA (CBM_{max}, M_{max} and T_{max}) are indicated in Table 3. As expected, the mean of up to 12 sites (M_{max}) gives the lowest value and an intermediate value is calculated for the mean of four sites in the bifurcation and distal common carotid arteries (CBM_{max}), whereas the highest value is obviously found for T_{max}. The distributions of CBM_{max}, M_{max} and T_{max} values are shown as histograms in Figure 1.

Figure 2 indicates the distribution of patients among the three strata defined according to the ELSA protocol. The very high prevalence (82%) of $T_{max} \geqslant 1.3$ mm (defined as 'plaques' according to the protocol) is evident, as is the low number of patients (n = 22, 1%) with normal carotid artery wall thicknesses (defined as $T_{max} < 1.0$ mm). The means of IMT measurements at common carotid and internal carotid sites were lower than that of measurements at the bifurcation ($P = 0.0001$, Wilcoxon test for dependent samples; Table 3). Overall the total number of discrete IMT measurements $\geqslant 1.3$ mm (plaques) for randomly allocated patients was 3721, with a median of two plaques per patient (range 0–11.5). The plaques were mostly found within the bifurcation (79.9%), then the internal (43.2%) and the distal common (36.7%) carotid arteries. Of randomly allocated patients, 18% had no plaque, 18% had one plaque only, 18% had two plaques, 15% had three plaques and 31% had more than three plaques.

Correlation of baseline carotid artery measurements to demographic and clinical characteristics of patients

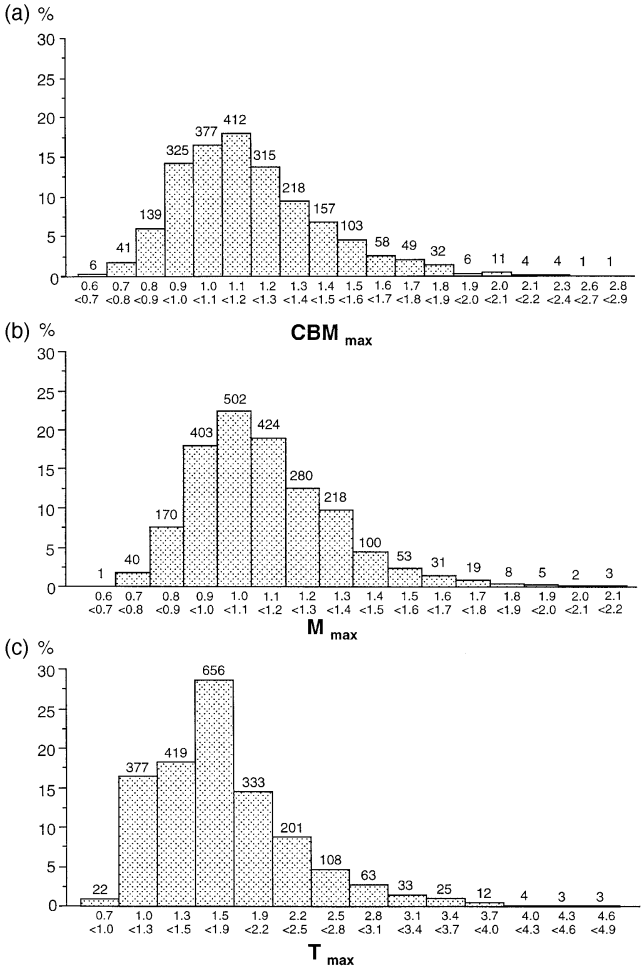
Correlation coefficients for relationships between baseline carotid artery IMT measurements and numbers of plaques per patient and various demographic and clinical characteristics of patients are listed in Table 4. In general the highest correlation coefficients were found when M_{max} (mean of measurements up to 12 sites) was used, but similar coefficients were also found when CBM_{max} (mean

Table 3 **Baseline patient characteristics: ultrasound variables**

	Mean	SD	Median	Range
CBM_{max} (mm)	1.20	0.26	1.15	0.65–2.83
M_{max} (mm)	1.13	0.21	1.10	0.70–2.12
T_{max} (mm)	1.80	0.58	1.67	0.88–4.83
IMT common carotids (mm)	1.04	0.17	1.02	0.67–2.10
IMT bifurcations (mm)	1.32	0.31	1.27	0.65–3.09
IMT internal carotids (mm)	1.02	0.28	0.95	0.43–3.19
Number of plaques per patient			2	0–11.5

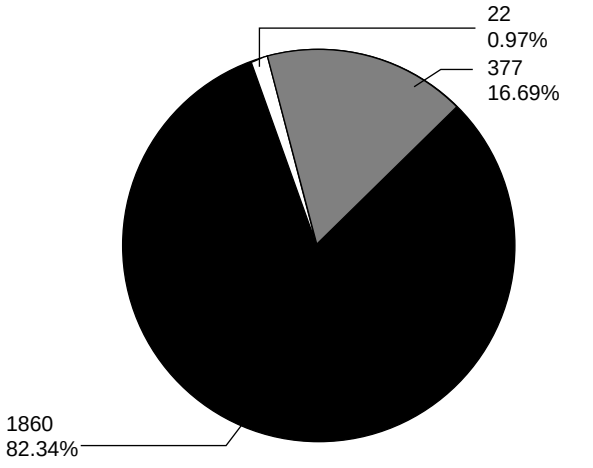
Duplicate baseline measurements in 2259 patients, performed prior to random allocation to treatment between visits 0 and 1. IMT, average intima–media thickness of measurements performed at the level of the distal common carotid, bifurcation and proximal internal carotid arteries, bilaterally; CBM_{max}, mean of the maximum of IMT of the four far walls of the carotid bifurcations and distal common carotid arteries; M_{max}, changes in the mean thickness of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid); T_{max}, overall mean maximum IMT.

Fig. 1



Distributions of baseline values of the means of the maximum intima–media thickness (IMT) of the four far walls of the carotid bifurcations and distal common carotid arteries (CBM_{max}, a), of the means of the maximum IMT at up to 12 sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid, M_{max}, b) and of the overall maximum IMT (T_{max}, c) for the entire population of patients randomly allocated to treatment in ELSA (n = 2259).

Fig. 2



Distribution of all patients randomly allocated to treatment in ELSA (n = 2259) among the three strata according to protocol (black area, plaque, patients with baseline $T_{max} \geqslant 1.3$ mm; grey area, thickening, patients with baseline $T_{max} = 1.0–1.3$ mm; white area, normal, patients with baseline $T_{max} < 1.0$ mm). Total numbers and percentages of patients by stratum are indicated.

of common and bifurcation measurements) was used. Correlation coefficients calculated for T_{max} (measurement at a single site) were somewhat lower. Correlation coefficients calculated for number of plaques per patient were generally intermediate between those calculated for M_{max} and those calculated for $T_{max.}$ The strongest associations were found for age, but highly significant correlations were also evident for SBP and pulse pressure, both when clinic and when 24 h ambulatory values were considered. Ambulatory values generally resulted in higher correlation coefficients. We found no significant correlation with DBP (either clinic or ambulatory values). For heart rate we found a statistically significant negative correlation to IMT measurements only when 24 h ambulatory values were considered. All lipid concentration measurements were correlated to carotid measurements (HDL in a negative way) but there was no significant correlation to glucose concentration and BMI. Correlations to creatinine concentration were of borderline significance. We found low, but statistically significant, correlations between duration of hypertension and carotid IMT.

Partial correlation coefficients were also calculated after adjustment for age. After adjustment for age, the correlations to duration of hypertension were no longer significant. Correlation coefficients for clinic SBP and pulse pressure were markedly reduced (from 0.20 to 0.12 and from 0.22 to 0.12 for M_{max}) though still remained highly significant. Correlation coefficients for ambulatory SBP and pulse pressure were also decreased by adjusting for age, but to a lesser degree (from 0.24 to 0.21 for 24 h SBP and from 0.35 to 0.23 for 24 h pulse pressure for M_{max}). Correlations for serum lipid concentrations were only slightly influenced by adjusting for age.

Correlations of carotid IMT measurements to non-continuous variables for patients were determined by calculating means and SD of CBM_{max} for stratified groups of patients. There was a clear influence of sex, in that men had CBM_{max} of 1.23 ± 0.26 mm and women had 1.16 ± 0.24 mm ($P = 0.0001$). Stratifying by smoking habit gave CBM_{max} values of 1.17 ± 0.25 mm in non-smokers, 1.21 ± 0.25 mm in smokers and 1.24 ± 0.28 mm in former smokers ($P = 0.0001$). Patients with previous cardiovascular diagnoses had CBM_{max} of 1.22 ± 0.26 mm, those with a non-cardiovascular diagnosis or no diagnosis had 1.19 ± 0.26 mm ($P = 0.0891$).

Table 4 **Correlative baseline data: carotid versus demographic and clinical measurements**

	CBM_{max}		M_{max}		T_{max}		Number of plaques per patient	
	r	Significance	*r*	Significance	*r*	Significance	*r*	Significance
Age	0.35	$P = 0.0001$	0.37	$P = 0.0001$	0.28	$P = 0.0001$	0.32	$P = 0.0001$
Body mass index	0.03	NS	0.04	NS	0.02	NS	0.01	NS
Duration of hypertension	0.09	$P = 0.0026$	0.12	$P = 0.0001$	0.07	$P = 0.0159$	0.09	$P = 0.0019$
Clinic SBP	0.19	$P = 0.0001$	0.20	$P = 0.0001$	0.13	$P = 0.0001$	0.16	$P = 0.0001$
Clinic DBP	−0.03	NS	−0.04	NS	−0.05	NS	−0.05	NS
Clinic pulse pressure	0.21	$P = 0.0001$	0.22	$P = 0.0001$	0.16	$P = 0.0001$	0.18	$P = 0.0001$
Clinic heart rate	−0.05	NS	−0.05	NS	−0.04	NS	−0.04	NS
24 h ambulatory SBP	0.23	$P = 0.0001$	0.24	$P = 0.0001$	0.18	$P = 0.0001$	0.21	$P = 0.0001$
24 h ambulatory DBP	0.03	NS	0.02	NS	0.02	NS	0.03	NS
24 h ambulatory pulse pressure	0.32	$P = 0.0001$	0.35	$P = 0.0001$	0.25	$P = 0.0001$	0.29	$P = 0.0001$
24 h ambulatory heart rate	−0.11	$P = 0.0001$	−0.13	$P = 0.0001$	−0.07	$P = 0.0229$	−0.10	$P = 0.0007$
Total cholesterol concentration	0.10	$P = 0.0005$	0.12	$P = 0.0001$	0.10	$P = 0.0009$	0.11	$P = 0.0002$
HDL cholesterol concentration	−0.08	$P = 0.0051$	−0.11	$P = 0.0001$	−0.09	$P = 0.0030$	−0.10	$P = 0.0003$
LDL cholesterol concentration	0.11	$P = 0.0001$	0.14	$P = 0.0001$	0.12	$P = 0.0001$	0.13	$P = 0.0001$
LDL : HDL cholesterol ratio	0.13	$P = 0.0001$	0.17	$P = 0.0001$	0.13	$P = 0.0001$	0.15	$P = 0.0001$
Triglyceride concentration	0.08	$P = 0.0038$	0.10	$P = 0.0004$	0.07	$P = 0.0209$	0.09	$P = 0.0020$
Glucose concentration	−0.02	NS	−0.00	NS	−0.00	NS	−0.02	NS
Creatinine concentration	0.05	NS	0.08	$P = 0.0038$	0.07	$P = 0.0209$	0.06	NS

Spearman correlation coefficients and *P* values for variables in Tables 2 and 3. Calculations are based on data from 1173 patients for whom complete sets of data were available. SBP, systolic blood pressure; DBP, diastolic blood pressure; CBM_{max}, mean of the maximum of IMT of the four far walls of the carotid bifurcations and distal common carotid arteries; M_{max}, changes in the mean thickness of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid); T_{max}, overall mean maximum IMT.

Table 5 **Multiple regression analyses of baseline carotid ultrasound measurements from demographic and clinical data for patients for whom complete sets of data were available**

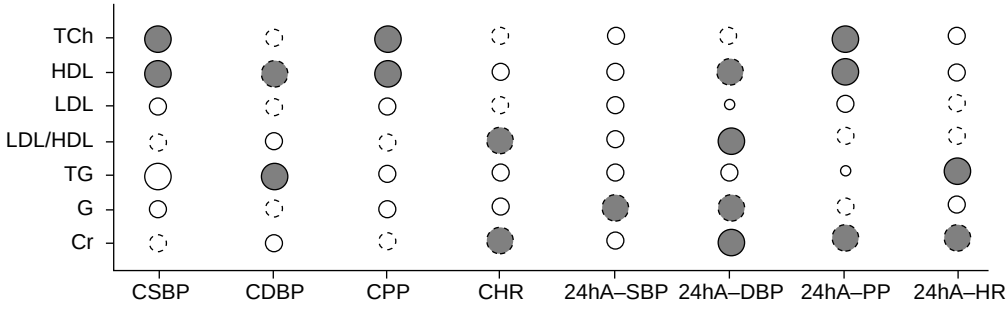
Variable	Standardized effect[a]			Significance (*P*)		
	CBM_{max} (n = 1544)	M_{max} (n = 1544)	T_{max} (n = 1537)	CBM_{max} (n = 1544)	M_{max} (n = 1544)	T_{max} (n = 1537)
Age	9.44	10.62	7.41	0.0001	0.0001	0.0001
24 h pulse pressure	6.95	8.10	6.25	0.0001	0.0001	0.0001
LDLC concentration	4.98	5.94	3.93	0.0001	0.0001	0.0001
Sex (male versus female)	4.80	7.44	5.00	0.0001	0.0001	0.0001
Triglyceride concentration	2.13	2.75	2.54	0.0331	0.0061	0.0110
Smoking						
Smoker versus non-smoker	3.34	4.06	3.84	0.0011	0.0001	0.0002
Smoker versus former smoker	0.78	0.60	1.03			
Clinic SBP	1.99	2.26		0.0472	0.024	
Body mass index			−2.09			0.0369

[a]Regression coefficient/standard error of regression coefficient; for categorical variables such as sex and smoking this is the effect of one category related to another category (indicated in brackets). LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; CBM_{max}, mean of the maximum of IMT of the four far walls of the carotid bifurcations and distal common carotid arteries; M_{max}, changes in the mean thickness of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid); T_{max}, overall mean maximum IMT.

Multiple regression analyses were performed as described in Methods. Reverse elimination by deleting variables with $P > 0.05$ gave the results shown in Table 5. The data in Table 5 refer to 1544 (1537 for T_{max}) patients (68% of all patients) for whom we had complete data on the variables selected. The analyses of Table 5 were performed on original values of IMT variables, without transformation. Age had the highest standardized effect, then 24 h ambulatory pulse pressure, then sex and then LDL cholesterol concentration. Triglyceride concentration, clinic SBP and smoking habits had lower standardized effects. On the whole, R^2 values were 0.179 for CBM_{max}, 0.235 for M_{max} and 0.123 for T_{max} for the patient population of Table 5.

Logarithmic transformation of IMT variables left the rank of all risk factors unchanged. Transformation to $1/\sqrt{CBM_{max}}$ and $1/\sqrt{M_{max}}$ again left the rank of the four major factors unmodified, but clinic SBP lost significant correlation, in favour of HDL cholesterol concentration. When the two strategies for substitution of missing values, mentioned in Methods, were implemented and multiple regression analyses recalculated for populations of 2240 and 1998 patients, respectively, the rank of the

Fig. 3



Spearman correlations of baseline metabolic variables to baseline blood pressure and heart rate. The size of each circle is proportional to the correlation; full circle, positive correlation; dashed circle, negative correlation; grey circle, significant correlation. The blood pressure and heart rate variables are indicated on the abscissae, the metabolic variables on the ordinates. TCh, total cholesterol concentration; HDL, high-density lipoprotein cholesterol concentration; LDL, low-density lipoprotein cholesterol concentration; LDL/HDL, LDL : HDL ratio; TG, triglyceride concentration, G, glucose concentration; Cr, creatinine concentration; CSBP, clinic systolic blood pressure; CDBP, clinic diastolic blood pressure; CPP, clinic pulse pressure; CHR, clinic heart rate; 24hA-SBP, 24 h mean ambulatory systolic blood pressure; 24hA-DBP, 24 h mean ambulatory diastolic blood pressure; 24hA-PP, 24 h mean ambulatory pulse pressure; 24hA-HR, 24 h mean ambulatory heart rate. From 1444 patients in whom complete baseline data were available.

standardized effects of the variables remained substantially the same as the one indicated in Table 5.

Correlations among metabolic variables, blood pressure and heart rate

All correlations were low, less than 0.09, with the sole exception of the correlation between 24 h ambulatory DBP and plasma creatinine level ($r = 0.15$). Although the level of statistical significance was occasionally attained, no haemodynamic variable was consistently and significantly correlated to all lipid variables. Magnitudes and statistical significances of the various correlation coefficients are indicated in Figure 3.

Discussion

Baseline ultrasound and blood pressure data from the ELSA cohort should be viewed as the set of initial data for the planned comparison to be performed at the end of this 4-year prospective interventional trial.

In that as many as 2259 hypertensive subjects have been allocated randomly, the ELSA is the largest available source of information about carotid artery wall alterations in hypertensive patients. It is also the only study providing a substantial amount of data on ambulatory blood pressure measurement in hypertension.

Carotid artery IMT and cardiovascular risk factors

Among the various demographic and clinical characteristics of ELSA patients, age has been found to have the most consistent and strongest correlations to all measurements of carotid IMT, confirming the importance of age as a determinant of IMT that had already been reported by authors of previous studies [19–24]. Significant correlations of IMT to SBP [19,20,22–24], male sex [19,21, 23–25], cholesterol concentration [19,22–25], triglyceride concentration [19], smoking [22–24] and previous cardiovascular disease [26] have also been reported. However, one of the most important findings of ELSA baseline data analyses is the important role played by blood pressure in accounting for differences in carotid wall thickness. In multiple regression analyses of the ELSA data a blood pressure measure, 24 h ambulatory pulse pressure, always ranked second to age, preceding in importance sex and LDL cholesterol concentration. The importance of blood pressure compared with that of LDL cholesterol concentration in ELSA might reflect the fact that our population was a selected one of hypertensive patients, and it is conceivable that LDL cholesterol concentration would have played a greater role for a population sample of hypercholesterolaemic subjects. It is also likely that the role of blood pressure could be studied better in ELSA than in previous studies, because of our in-depth use of ambulatory blood pressure monitoring, and because we considered pulse pressure in addition to SBP and DBP. In univariate correlation analyses the use of ambulatory blood pressure measurements regularly yielded higher associations with IMT than clinic blood pressure values and pulse pressure always yielded higher relationships than did SBP. In view of the importance traditionally given to DBP in guidelines for management of hypertension, it has to be noticed that DBP values in members of the ELSA population, even when calculated from ambulatory monitoring, had no relationship with carotid IMT.

Adjusting for age reduced correlation coefficients for SBP and pulse pressure, confirming the relationship of SBP with age. Relationships of ambulatory SBP and pulse

pressure values were less greatly reduced by adjusting for age; this is consistent with data from the PAMELA study [27], which showed that ambulatory SBP increases with age to a lesser extent than does clinic SBP.

In multiple regression analyses, 24 h ambulatory pulse pressure maintained an important role, indicated by its rank immediately after age and a standardized effects in the range 6.25–9.01 (standardized effect of age was 7.41–14.09). Clinic SBP was also a significant variable in multiple regression analyses, but with smaller standardized effects (1.99–3.74). The stronger correlation of pulse pressure than of SBP to carotid artery wall alterations supports the hypothesis that the pulsatile components of blood pressure have importance as a cardiovascular risk factor [28,29].

Plasma lipid concentrations were all significantly correlated to IMT measurements for the ELSA population, the correlation being negative, as expected, for HDL cholesterol concentration. The finding that adjustment for age only slightly affected these associations confirms that plasma lipid concentrations are hardly influenced by age, at least in the age range of the ELSA patients [30]. In multiple regression analyses LDL cholesterol concentration's association was regularly maintained, whereas that of triglyceride concentration was frequently retained but with a relatively low standardized effect (maximum 2.75). The standardized effect of LDL cholesterol level was in the range 3.92–6.23, being only slightly lower than that of sex (4.80–8.84). It is of some interest that plasma glucose concentration was not found to correlate to carotid IMT for the ELSA population, but uncontrolled diabetes was an exclusion criterion. The observation that correlations between serum creatinine concentration and carotid IMT were of only borderline significance might have resulted from the exclusion of subjects with serum creatinine concentrations > 1.7 mg/dl.

In the multiple regression analyses smoking persisted as a significant factor, though with standardized effects slightly lower than those of sex and LDL cholesterol concentration. It is interesting that there was no significant difference in IMT between smokers and former smokers. Previous antihypertensive therapy also did not provide any significant contribution to the results of multiple regression analysis. A history of previous cardiovascular disease had no significance as a risk factor in multiple regression analyses. However, a history of major cardiovascular disease was rare among ELSA patients because of our exclusion criteria.

Results of three recent studies in Finland [22–24] are consistent with the conclusions of our analysis of the ELSA population, insofar as all of them indicate that age is the most important predictor and SBP is a highly significant risk factor of carotid IMT.

Prevalence of carotid artery 'plaques' in hypertension

An interesting aspect of baseline observations in ELSA is the high prevalence of thickenings $\geqslant 1.3$ mm, defined as 'plaques' in the protocol. This was consistent throughout recruitment, with the prevalence of patients with 'plaques' in the range 82–83% when it was calculated after recruitment of 957, 1489, 1965 and 2259 patients. There was no great variation of prevalence among referral centres, prevalence ranging from 72% in Milan to 93% in Stockholm. 'Plaques' were more prevalent in the internal carotid and bifurcation than in distal common carotids.

When correlations between number of 'plaques' in individual patients and patients' characteristics were studied, we found significant associations with the same characteristics as those correlated to IMT average measurements, namely age, SBP and pulse pressure (however measured), LDL cholesterol concentration and LDL : HDL cholesterol ratio gave the highest correlation coefficients.

The high prevalence of 'plaques' in the ELSA population was not expected, since when the study was originally planned we had hypothesized that we would have found a similar proportion of patients with 'plaques', of patients with 'thickenings' and of patients with 'normal' carotids. Consequently, after recruitment of the first 1000 patients, a decision to redesign the study partially, by avoiding analyses based on strata and using baseline IMT measurements as continuous covariables, was taken.

Comparison of prevalence of 'plaques' in ELSA with prevalences in other interventional and observational studies is made difficult by the use of different definitions of 'plaque'. Among interventional trials, MIDAS investigators used the same definition of 'plaque' as that in ELSA, but the randomly allocated cohort was entirely made up of subjects with 'plaque', for the occurrence of 'plaque' was a criterion for inclusion in the trial [31].

A more valid comparison of VHAS and ELSA baseline data can be made, because in both studies patients were selected on the basis of similar criteria independently of the presence or absence of carotid wall alterations. Baseline patient characteristics were similar, with some higher SBP values (167.8 versus 163.6 mmHg) and slightly lower predominance of men (51.2 versus 54.3%) in VHAS than in ELSA. However, among VHAS subjects 39% of patients had 'plaques', 27% of patients had thickenings and as many as 34% of patients had normal carotid artery walls [9]. The definition of plaques in VHAS was much more conservative than that in ELSA (and than that in MIDAS) insofar as 'plaque' was defined as IMT > 1.5 mm. Indeed, if this criterion were applied to ELSA patients, prevalence of plaque would decrease to 63.8%. This is a good illustration of the effects of the arbitrary cut-off

criteria that are necessarily used to define carotid 'plaques'. The much lower percentage of patients with 'normal' carotid arteries in ELSA than in VHAS remains unexplained, however. It is not due to geographical factors: although ELSA was an international European study and the VHAS a purely Italian study, the prevalence of carotid artery alterations among ELSA patients recruited in Italy was similar to that among those recruited in other European countries. It should be remarked, however, that the upper limit of normality for IMT set both in ELSA and in VHAS was rather high and that a proportion of VHAS patients defined with 'normal' carotids was likely to have some wall thickening.

Comparing prevalence of 'plaques' in ELSA with data from observational studies is difficult, because of different definitions of 'plaque' used in other studies and different characteristics of the examined populations. In most cases an arterial plaque was defined as an echogenic structure encroaching into the vessel lumen with a distinct area and having an IMT more than 50% greater than that of neighbouring sites. According to this definition, prevalence of plaques among hypertensive patients was found to be 23–96%, according to patient characteristics [23,32–36]. In most of these studies, age, history of hypertension, history of smoking, cholesterol concentration and systolic blood pressure were significantly correlated to number or extent of plaques [23,32,36], supporting the data from ELSA. In the Kuopio Ischaemic Heart Disease Risk Factor Study [37] the prevalence of carotid plaques among men with sitting SBP $\geqslant$ 175 mmHg was 2.61-fold greater than that among men with lower SBP. Likewise, in the Atherosclerosis Risk in Communities (ARIC) study [38] hypertension was associated with an adjusted odds ratio for ultrasound evidence of carotid atherosclerosis of 2.9 relative to normotensive individuals.

Are carotid artery wall alterations related to atherosclerosis?

It appears quite interesting that, in the analysis of ELSA baseline data, all major known risk factors for atherosclerosis have been found to be correlated to the various IMT measures used as end points in the trial and to the number of 'plaques'. However, current ultrasound techniques cannot clearly distinguish between media and intima and all measurements reflect the intima–media complex. At present it is not possible to determine whether an increase in IMT is a result of medial hypertrophy and thus represents carotid artery localization of a more widespread hypertension-related phenomenon or whether it is the expression of intima thickening, thus being an early manifestation of atherosclerosis [39]. Although no definite answer to this crucial question can be given at present, the latter interpretation is favoured by the fact that thickenings are predominantly located in the bifurcation (which is known to be the preferred site for atherosclerotic lesions) and by the discrete nature of these thickenings, which makes their definition as 'plaques' reasonable. The correlation between carotid artery IMT and 'plaques' on one side and coronary events and strokes on the other found both retrospectively [19] and prospectively [40] lends further support to the assumption that at least part of the increase in IMT frequently found in hypertensive patients is related to atherosclerosis.

Correlations between blood pressure values and metabolic variables

The lack of consistently significant correlations between blood pressure values (including ambulatory blood pressure) and plasma lipid concentrations deserves a brief comment, because this seems to be in contrast to a recent analysis by Goode *et al.* [41] of data provided by a number of large epidemiological studies in which some correlations, particularly between SBP and total cholesterol and triglyceride concentrations, have been found. As a matter of fact, some occasional correlations, including those between clinic SBP and pulse pressure and total cholesterol concentration, have also been found for the ELSA patients, but the observations that only ambulatory pulse pressure and not ambulatory SBP maintained a significant association with total cholesterol concentration and that no blood pressure measurement was ever significantly correlated to LDL cholesterol concentration injects some reasonable doubt. However, most of the epidemiological studies analysed by Goode *et al.* [41] were much larger than ELSA and, furthermore, patients with serum total cholesterol or triglyceride concentrations > 300 mg/dl were excluded from ELSA. Likewise, the weakness of the expected correlation between blood pressure values and serum creatinine concentration might have resulted from the exclusion of patients with serum creatinine concentrations > 1.7 mg/dl.

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